Journal Club

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Flexible Adaptation of Brain Networks during Stress

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Review of Young et al.

How does the brain coordinate efforts to meet environmental challenges? Although research over the past century has illuminated specific details of stress signaling pathways, less well understood is how global patterns of neural activity fit with this prior research to explain how an organism flexibly adapts to changing life circumstances.

In the past several years, there has been a growing movement to study ensembles of neurons whose functional outputs are greater than simply the sum of their component neurons (Yuste, 2015). This line of inquiry has led to the identification of a number of brain "networks" described through coherent connectivity using fMRI. Common networks include the following: (1) the default mode network, associated with self-referential processing; (2) the central executive network, associated with cognitive processing; and (3) the salience network, associated with orienting attention to contextually relevant stimuli (Bressler and Menon, 2010). Questions remain, however, about how these distinct networks interact in the service of generating complex behavioral responses in real time.

Complex behavioral responses are particularly necessary in responding under stress. Stress can be defined as the subjective interpretation of adverse changes in the environment, leading to an orchestrated cascade of neural and endocrine signals intended to enable an organism to adapt to environmental demands (Joëls and Baram, 2009; Ulrich-Lai and Herman, 2009). Researchers have suggested that, in response to stress, the salience network may play a key role in coordinating dynamics of other networks, but until recently, it was unclear how this process might unfold (Bressler and Menon, 2010; Chen et al., 2016).

In a recent article, Young et al. (2017) provided insight into interactions between these large-scale brain networks as a function of arousal on a moment-by-moment basis. Young et al. (2017) recruited healthy adult men to undergo fMRI scanning while watching a video clip that showed increasingly aversive content over time. The clip heightened arousal in participants as indicated by increases in heart rate, cortisol, and blood pressure over the course of the film. Another group of participants watched the movie outside of the scanner and provided continuous arousal and valence ratings. There was a strong negative correlation between valence and arousal throughout the clip, indicating that arousal was highest when subjects were experiencing intense negative emotion.

Next, fMRI time series data were extracted from all voxels within the salience, executive control, and default mode networks. Young et al. (2017) evaluated network cohesion, which measures the tendency of all voxels within a given network to display similar behavior (e.g., increasing in activity at the same time). Cohesion within the salience network increased linearly with increasing heart rate (Young et al., 2017, their Fig. 4). This demonstrated that the approach could assess unfolding network changes on a moment-by-moment basis, and indicated that the primary measure of arousal was correlated with salience network activity (Young et al., 2017).

Between-network cohesion was also assessed, and it was discovered that cohesion between the salience and executive control networks had a negative quadratic relationship with heart rate. In other words, cohesion was greatest at moderate levels of arousal and dropped off at higher or lower levels of arousal. No associations were found between the default mode network and either of the other two networks.

Although the study did not address how arousal alters interactions between brain networks, previous work suggests that neuromodulators are likely to play a role (Bouret and Sara, 2005). Notably, both norepinephrine (NE) and dopamine are associated with stress signaling (Arnsten, 2009) and may link salience network activity with executive control network activity. Stress-related changes in noradrenergic activity have been shown to influence activity in the salience network (Hermans et al., 2011). And both NE and

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dopamine impact prefrontal cortex network function in an inverted-U-shaped manner (Arnsten, 2011), mirroring the inverted-U-shaped relationship identified by Young et al. (2017) between heart rate and cohesion of the salience and executive control networks (their Fig. 5). Furthermore, NE neurons in the locus ceruleus change their firing rate to ensure that NE levels are optimal for coordinated PFC function at moderate arousal conditions (Arnsten, 2011). During alert nonstressed waking, relatively low NE levels activate primarily high-affinity α2-adrenergic receptors, which promote working memory performance, whereas during stress, high levels of noradrenaline activate lower-affinity α1-receptors and β1-receptors, which suppress neuronal firing in the PFC, therefore favoring more reflexive subcortical signaling (Arnsten, 2009, 2015; Wirz et al., 2017). α2-Adrenergic signals might generate coherence between the salience and executive control networks at moderate levels of arousal, by optimally tuning neuronal firing in the PFC to enhance prefrontal network connectivity with other networks.

While filling a gap in the literature, the results by Young et al. (2017) also raise important questions about the relationship between often-correlated elements of stressful environments. One or multiple elements could be driving the observed effects. Young et al. (2017) suggest that their results are driven by arousal itself, and it is possible that arousal increases network coherence between the executive and salience networks through the neuromodulatory signaling cascade described above. In support of alertness/arousal driving the observed effects, a recent study using Human Connectome Project data found that shifting from rest to task engagement, across a variety of cognitive, social, and emotional tasks, led to enhanced salience and executive control network activity (Bolt et al., 2017). Although this interpretation is a parsimonious one, it is also plausible that valence rather than arousal is driving the observed effects. There is evidence to suggest that valence and arousal result from distinct neurobiological pathways (Kim et al., 2013) and can have differential effects on cognitive function (Woodson et al., 2003; Kuhbandner and Zehetleitner, 2011). In Young et al. (2017), arousal and valence were correlated (their Fig. 3), creating a pairing of high arousal and negative valence (e.g., fear), so it is unknown whether network cohesion might vary under conditions where arousal and valence are orthogonal, for example, in cases of low arousal and negative valence (e.g., sadness) or in situations of high arousal and positive valence (e.g., excitement).

Another important note in interpreting the results of Young et al. (2017) is that, although the authors describe a link between salience network activity and executive function, whether these effects generalize to most stressors is an open question. A stressful yet less cognitively demanding task, such as a cold-presser stress task where subjects hold their hand in a bucket of ice water, might not engage the executive network in the same way. Furthermore, although Young et al. (2017) draw conclusions about executive function, they did not report a behavioral measure of executive function in the paper. Although this cautions any interpretation of behavioral implications of the findings, the narrative of Young et al. (2017) about the salience network affecting cognitive function is consistent with prior studies linking executive control network connectivity to executive task performance (Seeley et al., 2007). And as mentioned previously, the results fit with robust evidence that stress has an inverted-U-shaped relationship with behavioral indices of executive function (Arnsten, 2009). Furthermore, a recent study (Chen et al., 2016) found that temporal flexibility within the salience network predicts cognitive flexibility (processing speed, executive function/cognitive flexibility, and executive function/inhibition), suggesting that momentary changes in salience network activity are likely to result in similarly dynamic changes in cognitive processing.

This work could have important implications for the study of stress-related mental disorders, and future work should focus on individuals diagnosed with stress-related psychopathology. Disruptions in salience network signaling alone or in conjunction with disruption in other networks occur in a range of psychiatric disorders from depression and anxiety to schizophrenia (Menon, 2011). A possible extension of the work could be in guiding studies using transcranial magnetic stimulation (TMS) for the treatment of depression, as there is some evidence that network connectivity predicts clinical outcome of TMS treatment (Fischer et al., 2016). Whereas most treatment studies using TMS focus on the executive control network, the present results suggest that targeting salience network activity may be a promising avenue for future treatment-based research.

In conclusion, the results of Young et al. (2017) help to integrate studies of stress-related neuromodulatory signaling and behavioral studies of stress-related executive functioning through an insightful investigation of large-scale brain network dynamics. Their primary finding is that salience network and executive control network activity are most in sync at moderate levels of heart rate/arousal. The result dovetails with physiological studies of catecholamine signaling under stress, raising the possibility that α2-adrenergic signals might generate coherence between the salience and executive control networks at moderate levels of arousal. Future work can help to directly link the neuromodulatory and network-based literatures, clarify the role of valence and task-demands in driving these effects, and investigate their impact on generating flexible behavioral outcomes. Finally, the results lay the groundwork for future clinical investigations targeting salience network activity for the treatment of stress-related disorders.

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